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Appln No.: 10/555,860 Docket No.: 27519-0012US1 Inventor: Christopher P. Holmes et al. NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL) MODIFIED PEPTIDE BASED COMPOUNDS

Synthesis of H-TAP-Boc molecule

NEW SHEET

Synthesis of Cbz-TAP

Synthesis of Cbz-TAP-Boc

Synthesis of Boc-TAP

FIG. 1C

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Attaching Spacer to Peptide with C-Terminus

Peptide with free C-terminus:

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Attaching Spacer to Peptide with Free Side-Chain Acid

Peptide with free side-chain acid:

PEGylation of Peptide, with mPEG-NPC

Peptide with TAP on C-terminus:

FIG. 4B

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MODIFIED PEPTIDE BASED COMPOUNDS NEW SHEET

PEGylation of Peptide, with mPEG-SPA

Peptide with TAP on C-terminus:

FIG.5A

mPEG-SPA

FIG.5B

Attaching Spacer and Synthesizing Peptide

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Synthesis of Peptide Dimer with Spacer, Attached to Resin Synthesis of TentaGel-Linker:

FIG.7A

Synthesis of TentaGel-Linker-TAP(Boc)

FIG. 7B

Synthesis of TentaGel-Linker-TAP-Lys

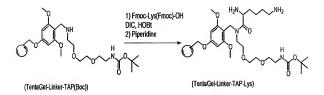


FIG.7C

Synthesis of TentaGel-Linker-TAP-Lys(Peptide) 2

Peptide

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Cleavage from Resin

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Oxidation

Dimeric peptide (XYZ) containing reduced cysteine residues

Dimeric peptide (XYZ) containing oxidized disulfide bonds

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PEGylation of Peptide Dimer with Spacer, with mPEG-NPC

FIG. 8B

 $O(O)_{n}$ $O(O)_{NO_{2}}$

mPEG-NPC

FIG.8C

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PEGylation of Peptide Dimer with Spacer, with mPEG-SPA

FIG.9A

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Ion Exchange Purification

FIG. 10

m=1-5, n=1-14, m and n are integers

FIG. 11A

FIG. 11B

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m=1-5, n=1-14, m and n are integers

FIG. 11C

$$\begin{array}{c} X \\ O \longrightarrow (CH_2)_m \\ N \\ BocHN \longrightarrow (CH_2)_m \\ O \longrightarrow X \end{array}$$

m=1-5, n=1-14, m and n are integers

FIG. 12A

$$X = OH O-N O-NO_2$$
, or $O = F$

FIG. 12B

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m=1-5, n=1-14, m and n are integers

FIG. 12C

Synthesis of Homotrifunctional Molecules
Branched homotrifunctional molecules having the structure

m=1-2, n=1-6, m and n are integers

$$X = OH O-NO_2 OF FF$$

FIG. 13A

m=1-2, n=1-6, m and n are integers FIG. 13B

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

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C-Terminus Dimerization and PEGylation Using A Trifunctional Molecule A trifunctional molecule having the structure

FIG. 14A

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FIG. 14B

Ac-I-E-G-P-T-L-R-Q-W-L-A-A-R-A

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N-Terminus Dimerization and PEGylation Using A Trifunctional Molecule

FIG. 15A

FIG. 15B

FIG. 15C

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MODIFIED PEPTIDE BASED COMPOUNDS NEW SHEET

FIG. 15D

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)
MODIFIED PEPTIDE BASED COMPOUNDS

A trifunctional molecule having the structure

FIG. 16A

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL)

MODIFIED PEPTIDE BASED COMPOUNDS

FIG. 16B

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NOVEL SPACER MOIETY FOR POLY(EHTYLENE GLYCOL) MODIFIED PEPTIDE BASED COMPOUNDS

NEW SHEET

FIG. 16C

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FIG. 16D